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Häfner, Sophia Julia

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Highlights

The many (sur)faces of B cells

Sophia Julia Häfner

University of Copenhagen, BRIC Biotech Research & Innovation Centre, Anders Lund Group, Ole Maaløes Vej 5, 2200 Copenhagen Denmark

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ABSTRACT

This issue of the *Biomedical Journal* is dedicated to the latest findings concerning the complex development and functions of B lymphocytes, including their origins during embryogenesis, their meticulous control by the CD22 receptor and different types of T cells, as well as the immunosuppressive abilities of certain B cell subsets. Furthermore, we learn about the complicated genetic background of a rare cardiac disease, the surgical outcomes of pure conus medullaris syndrome and occurrences of tuberculous spondylitis after percutaneous vertebroplasty. Finally, we discover that brain waves could very well be used for biometric authentication and that diffusion imaging displays good reproducibility through a spectrum of spatial resolutions.

Spotlight on reviews

The many (sur)faces of B cells

Frequently, when it comes to scientific discoveries, the idea precedes substantially the concrete material proof: exhibit A - the idea that immunity could be mediated by circulating "antitoxins" was stated in 1890 by von Behring and Kitasato [1], followed by the hypothesis that these antitoxins were secreted by cells covered in antibody receptors formulated by Nobel prize winner Paul Ehrlich in 1908, while the experimental delineation of B and T cells only took place in 1965 [2].

Nowadays, B cells are one half of the must-know about adaptive immunity, together with the facts that they produce antibodies and cytokines, or operate as antigen-presenting entities for T cells (Fig. 1).

Beyond this lies the more intimate life of B lymphocytes, to begin with their very name, actually. Although it would intuitively make sense, the "B" does not refer to the bone marrow, where B cells indeed mature in mammals, but to the "bursa of Fabricius", an obscure bird-specific gland located over the terminal part of the avian gut, whose function remained unknown for more than three centuries. It took a mixture of curiosity and serendipity to unravel its true nature, and additionally lend immunology a huge hand: "What is its function?" "Good question, you find the answer", this is how Bruce Glick remembers his first encounter with the bursa in 1952. He took up the challenge and the bursa out of countless chicks, with little effect on their development. The story could have ended there, hadn't Glick's colleague Timothy Chang borrowed a few random chickens in order to demonstrate immunisation to his students and been rather upset about the very un-cooperative animals, which died instead of nicely

E-mail address: sophia.hafner@bric.ku.dk.
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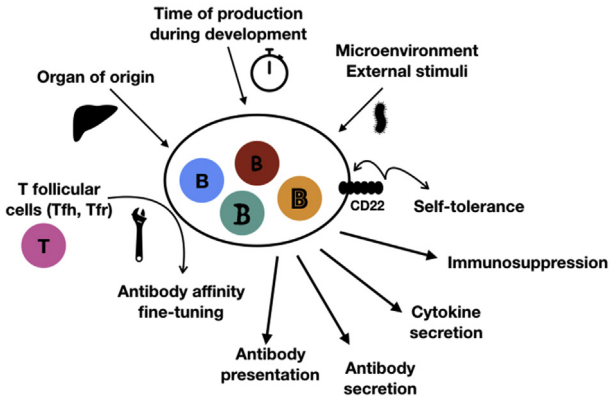

Fig. 1 **The B cell universe is permanently shaped by countless cues.** A very simplified summary of the elements shaping the manifold flavours of B lymphocytes discussed in this issues' reviews. During embryonic development, different waves of progenitors from various sites of origin give raise to different B cell progenies [3], while B cell maturation in turn is fine-tuned and controlled by different populations of T follicular cells [4]. CD22 binding to glycans ensures self-tolerance [5] and several subsets of B lymphocytes exert themselves immunosuppressive functions [6].

producing antibodies. However, after verification, all chickens that failed to make antibodies lacked a bursa [7].

The connection was quickly made, and given the disinterest of the big journals in ornithological matters, it got published in *Poultry Science* in 1956 and initially nearly forgotten [8].

Another secret chord on the B cell's bow started to be unveiled only in the late 90s, when it became clear, that certain subsets of B lymphocytes displayed suppressive functions in autoimmune and inflammatory contexts [9].

Immunosuppressive functions of the adaptive immune system, such as immune tolerance of the self, were originally mainly ascribed to a specific type of T cells, termed Treg cells, which mediate tolerance to self-antigens and counteract excessive inflammation [10]. Yet the increasing abundance of mouse models for impaired immune functions and diseases made it clear that B cells hold the power to attenuate inflammation *via* the production of interleukin 10 (IL-10) [11].

Simon Fillatreau has been at the forefront of the elucidation of the B cells' suppressive function since over 17 years and contributed with cornerstone experiments to the field, such as the proof that recovery from experimental autoimmune encephalitis (EAE) in mice depends on autoantigen-reactive B cells competent for IL-10 production in 2002 [11]. Through his review in this issue of the *Biomedical Journal*, Fillatreau comprehensively describes the different immunosuppressive B lymphocyte subsets identified by now and how they can be either friend or foe in various disease settings, carefully pointing out similarities and divergences between man and mouse [6].

The first part of the review extensively focuses on the attempt to describe the various subsets of IL-10-producing B cells, most of them found in the spleen, *via* different surface marker combinations. The immunosuppressive abilities of each group is functionally certified by adoptive transfer experiments, that is their transfer from an animal in remission after a strong inflammatory challenge into an animal about to be exposed to this challenge, in order to verify if the inflammation will be better kept in check in the recipient individual.

Fillatreau discusses notably ambiguous markers such as CD1d or tumour necrosis factor receptor 2 (TNFR2), as B cells expressing these can secrete anti-inflammatory IL-10 as much as pro-inflammatory IL-6. Moreover, he explains how several surface receptors could serve as markers for immunosuppressive B lymphocytes and play a concrete role in their activation and/or function. Tetraspanin (CD9), for example, is broadly expressed by all types of leukocytes and required for all types of cell adhesion and signalling [12], but might also tag the most competent IL-10 producing B cells. The T cell Ig domain and mucin domain protein 1 (TIM-1) in turn recognises apoptotic cells and promotes IL-10 secretion by activated B cells, thus eventually transforming danger signals from excessive inflammation into a trigger to dampen the latter.

This serves as a logical transition into an account of the various signals that can awake or delay a suppressive potential in certain B cells, such as B cell receptor (BCR) activation, certain cytokines or hypoxia. The author notably stresses the fact that several elements in specific order might be required for a successful activation process.

Having already hinted that an increasing potential for IL-10 secretion seems to correlate with the differentiation of B cells into antibody-secreting cells (ASCs), namely after TNFR2 activation, the author discusses subsequently the regulatory function of plasma cells, terminally differentiated B cells that secrete large amounts of antibodies. Surprisingly, some immunosuppressive plasma cells originate not from the spleen but from the small intestine lamina propria. As a new element of the “gut-brain-axis” [13], IgA isotype plasma cells seem to migrate into the central nervous system (CNS) after EAE induction in mice, for instance.

This is not necessarily good news, nonetheless. IgA-expressing plasma cells have been shown to hamper CD8 T cells during their anti-tumour activities in prostate cancer models and hepatocellular carcinoma. In times where immunotherapy bears massive hopes for cancer treatment on its shoulders, preventing the immune system from developing a tolerance towards the tumour is of crucial importance, thus the precise characterisation and study of this B cell subset represents valuable information.

In line with the “foe” side of regulatory plasma cells, Fillatreau finally acquaints the reader with a very specific subset of the latter, harbouring a very distinct pattern of surface markers, transcripts, epigenetic profiles and BCR repertories. These cells appear to develop quickly from pre-existing plasma cells and suppress the early innate immune response mediated by neutrophils and natural killer cells, thus retarding for example bacterial clearance.

In conclusion, the author stresses the remarkable increase in knowledge concerning the complex population of immunosuppressive B cells that has been gained over the last two decades, but equally stresses the gaps in understanding that require to be closed before specific cell subsets could be

modulated in the context of autoimmune or inflammatory diseases as well as for cancer immunotherapy.

Spotlight on original articles

The complex genetic background of Brugada syndrome

On the dot with the turn of the millennium, the high throughput sequencing revolution took off with the - laborious, at that time - deciphering of the human genome. Since then, the costs of the procedure have dropped exponentially, while the experimental speed and feasibility rocketed, bringing about a substantial amount of surprises [14]. One of them was the realisation of the complicated DNA-to-disease connection. Instead of clear-cut links leading from specific mutations or sequence variants to distinct diseases, an impressive number of susceptibility elements was identified and the conclusion drawn that most disorder phenotypes can originate from many combinations of genetic, epigenetic and life-style related causes [15]. The other major finding was the massive amount of non-coding transcripts being produced from the genome, and how much they matter. Although the discovery of small non-coding RNAs, notably microRNAs (miRNAs) had already consolidated the observation that actually all RNA species are non-coding, but one, only the boom of long noncoding RNAs a couple of years ago fully unfurled the realisation that non-coding regions, by their very sequence or their transcripts, are far from junk DNA, thus also giving miRNA research a new boost {Jarroux:uh}.

Daimi et al. elegantly manage to make both elements meet in their present study about the genetic elements underlying a cardiac disorder [16].

Brugada syndrome (BrS) is a very rare genetic disease affecting the electrical activity of the heart, specifically characterised by a coved-type-ST-segment elevation of at least 0.2 mV followed by a negative T wave on the electrocardiogram (ECG) [17], a feature that can be detected either spontaneously or unmasked by a drug-induced sodium channel blockade, for example with flecainide. The consequence is an elevated risk of arrhythmic events and sudden cardiac death [18], which can be limited by the implantation of a cardioverter defibrillator or administration of quinidine. Familial linkage led to the conclusion that BrS is inherited in an autosomal dominant manner, skewed towards male and Asian individuals, however the exact genetic determinants are manifold. Most of them affect the cardiac sodium channel Nav1.5, required for the initial upstroke of the action potential. “Most”, hover means in this case that only about 20% of BrS cases are caused by close to 400 different known mutations of the SCN5A gene, and even the complete current set of 17 susceptibility genes only explains maximally 40% of cases [19].

The authors briefly introduce the reader to the clinical profile of their test subjects, seven members of a Tunisian family, and their classification into symptomatic, asymptomatic and no BrS patients, asymptomatic meaning that the typical ECG defect was only revealed *via* flecaidine induction.

Subsequently, they proceed to the genetic analysis of the family members, focusing for obvious reasons first on the entire SCN5A gene, but including, unlike previous studies, the 5′UTR and 3′UTR regions.

Interestingly, aside from two very well known and studied polymorphisms associated with BrS, the authors detect a new missense variant in the SCN5A coding region, which seems not to be present in a control population and could theoretically impact on the function of the sodium channel or its transport to the cell membrane. Yet, following the overall scheme of susceptibility genes, this mutation does not perfectly correlate with the presence or absence of the disease.

However, the following scrutiny of the 3′UTR region harbours more compelling findings in the form of five polymorphisms, which were previously reported yet not associated with BrS. Daimi et al. immediately make the connection with the frequent location of miRNA binding sites in the 3′UTR, and indeed, two polymorphisms create new binding sites for miR-1270, a rather poorly conserved microRNA. Previous reports suggested that the latter might interact with interferon-α1, as well that it is associated with poor prognosis in osteosarcoma [20].

Logically, increased binding of miR-1270 should decrease SCN5A mRNA and protein levels, thus ultimately leading to an insufficient amount of channels in the cell membrane. In line with this hypothesis, the authors demonstrate that the overexpression of miR-1270 in cultured cardiomyocytes reduces as expected SCN5A mRNA amounts.

A glance at five other BrS susceptibility genes only revealed already known polymorphisms, thus Daimi et al. return their attention to microRNAs, more specifically to the set of miRNAs known to somehow regulate SCN5A. A genetic screen of their precursors and flanking regions in the family members revealed a single nucleotide polymorphism (SNP) 36 base pairs upstream of the miR-219a precursor sequence. Mainly miR-219-5a has been related to tumour suppressor activities [21] and the regulation of neuronal apoptosis [22]. In a previous study, the authors demonstrated that miR-219a overexpression increases strongly SCN5A expression [23]. Thus, if the SNP in question decreases miR-219a expression, this could contribute, to a lower SCN5A expression and the potential development BrS.

After a comprehensive summary of their observations, the authors insist on the necessary caution when it comes to their interpretation. They argue for BrS to be determined rather by an additive rather than a single variant effect. Furthermore, they encourage strongly a more thorough investigation of the non-coding regions and surroundings of candidate genes, as well as to take into account the interplay with other processes, such as aging for example, in order to complete the complex, modular puzzle of elements that constitute BrS.

Also in this issue

Introduction to the development of humoral immunity

There is an evident leitmotiv to the four very instructive reviews in this issue of the *Biomedical Journal*, as they all embrace the state of the art regarding the development and biology of B lymphocytes, ranging from the development of the B cell

compartment during embryogenesis [3] to the selection and differentiation of germinal centre B cells by T lymphocytes [4]. Jean Kanellopoulos and David Ojcius succeed to summarise all four subjects in a very succinct and informative manner in their introduction, providing the reader with essential information and the appetite for more information [24].

Reviews

The B cell arsenal has many origins in space and time

As it has become clear in the spotlighted review by Fillatreau, B cells come in many flavours, with major functional differences [6]. Which raises naturally the question when these differences are established, or primed. The obvious answer would point towards the continuous production of circulating blood cells from bone-marrow-derived haematopoietic stem cells (HSCs) throughout the life of the organism. Yet Elsaid et al. draw attention to several specialised lymphocyte populations that are produced only during a limited time during embryonic development and subsequently migrate to various tissues, where they self-renew, contribute to tissue homeostasis and fight pathogens independently of the HSC system [3]. Backed up by numerous mouse model and lineage tracing experiments, the authors thoroughly discuss the diverse origins and commitment routes of B cell subsets during embryogenesis, and the main transcriptional regulators in charge of steering the process, especially the earliest molecular cues for a B-cell *versus* T cell bias signature. They stress namely the fact that identity acquisition happens at sequential stages of differentiation, and not in a binary manner. Other differentiation signals emanate from the foetal hematopoietic microenvironment, such as the cytokine IL-7 in the foetal liver and later in the thymus. This review clearly depicts how the combination of sequential cell production and signalling events plus varying microenvironments gives raise to the stunning diversity of the immune system (Fig. 1).

How the CD-22 co-receptor ensures self-tolerance in B cells

The dark side of B cells surfaces in many autoimmune disorders, such as rheumatoid arthritis, when autoreactive B cells escape central tolerance, normally established in the bone marrow [25].

Enterina et al. focus on one particular element in the arsenal of tools meant to keep them at bay, a co-receptor found on B cells named CD22, which antagonises BCR signalling [5]. Much conveniently, the patterns of cell surface glycosylation differ markedly between vertebrates and pathogens. Glycan capping by sialic acid for example is a rather vertebrate-specific trend, and thus a great landmark for immunological self-recognition. CD22 namely recognises α2-6 sialic acids on glycoconjugates, either in *cis* on the same cell surface, or in *trans* on other cells. Recapitulating all molecular mechanisms essential for the understanding of their theories, the authors explain why the spatial arrangements of CD22, BCR and ligands on the cell surface matter. Indeed, *cis*-ligands modulate the formation of CD22 homo-nanoclusters and keep CD22 away from the BCR, while *trans*-ligands seem to drag the receptor into the immunological synapse, where it inhibits the activation of B cells (Fig. 1). Meanwhile, therapeutic hopes are nurtured by the observation that liposomes targeting antigen-specific BCR and CD22 combinations can decrease unwanted B cell activities, yet many open questions on variations in CD22 behaviour during development and its roles in different processes persist.

Fine-tuning of B cell maturation by different T follicular cells

Aloulou et al. round up the collection on B cells with an elaborate account on how T cells shape the selection and differentiation of germinal B cells, a process key to the development of memory B cells during immunisation [4] (Fig. 1). The first part of the review is dedicated to T follicular helper (Tfh) cells, specifically expressing Bcl-6, and their intricate crosstalk with maturating B lymphocytes in the B cell area in lymphoid follicles. Communication involves numerous ligands and receptors, but also cytokines, such as the key regulator of the germinal centre, IL-21. The authors underline the heterogeneity of the Tfh compartment, including several phenotypically and functionally distinct subsets of circulating Tfh cells.

In a second section, Aloulou et al. focus on T follicular regulatory (Tfr) cells and their heavy responsibility to ward off the emergence of auto-reactive B cells, while also fine-tuning the quality of selected B cells. After a detailed description of the origins and features of Tfrs, the authors discuss how their modulation of antibody affinity could be protective just as much as deleterious, and finally emphasise the importance of understanding how Tfh and Tfr cells react to environmental cues, with the ultimate goal to improve vaccine strategies.

Original articles

Show me your brain waves, and I tell you who you are

Human individuals display many unique phenotypic features - the pattern of the finger friction ridges or the retinal blood vessels, the combination of multiple DNA short tandem repeat alleles, or dental profiles. All of these are currently used for authentication purposes, from unlocking a smartphone to identifying a criminal [26]. Brainwaves [27] or heartbeat patterns [28] however are not (yet) the first guess when it comes to biometric applications.

Wrong, claim Zeynali et al., because electroencephalogram (EEG) signals display individually distinctive patterns, which are easy to measure but difficult to steal or to obtain by force, and literature proves that quite some effort is made in the domain [29].

In their study, the authors focus on the optimisation of a user-friendly single channel authentication system with high accuracy [30]. By testing different channels on various mental activities combined with several types of machine learning, they achieve a unprecedented mean accuracy of over 97% and conclude that the neural network classifier and the O2 electrode perform best within this system.

Maybe the next iPhone will come with an electrode.

Diffusion imaging displays good reproducibility at different spatial resolutions

What could whipped cream possibly have in common with the human brain? More than one could think, at least when it comes to diffusion-weighted magnetic resonance imaging (DW-MRI), a technique that measures the diffusion process of water molecules in biological tissues [31]. It turns out that the

diffusion coefficient of whipped cream is quite similar to the one of the brain, and that the coexistence of fat and water mimic accurately a heterogeneous system, allowing for compartmental diffusion. The latter takes place in living tissues, given that the cellular architecture limits free diffusion, DW-MRI allows for example for a very accurate mapping of axonal trajectories and white matter connectivity [32], and due to its sensitivity to the cellular environment, it can detect early pathologic changes. These assets have made it a valuable tool for the study of neurological diseases, monitoring of the damages caused by stroke and more recently also for the staging of non-small-cell lung cancer [33].

In order to make sure that DW-MRI measurements are reproducible over a certain range of spatial resolutions, Chen et al. scanned both whipping cream phantoms and rats with different voxel sizes while controlling the signal to noise ratio [34]. They come to the satisfying conclusion that the measured values are stable and reproducible through the range of voxels.

Impact of pure conus medullaris syndrome on voiding and sexual satisfaction

The conus medullaris is located at the end of the spinal cord and injury of the latter and the lumbar nerve roots can lead to the loss of bowel and bladder reflexes, sexual dysfunction, numbness and lower limb motor weakness, termed conus medullaris syndrome (CMS) [35]. Pure CMS excludes lower limb weakness, but still represents a major loss of life quality for the patients. In order to assess the level of recovery after surgical and adjacent treatment, Chiu et al. performed a retrospective review on eight patients with pure CMS following thoracolumbar fractures caused by falling accidents [36]. They recorded that half of the patients regained a normal voiding and sexual function, and that a better recovery correlates with an earlier medical treatment, including surgery.

Rare cases of tuberculous spondylitis after percutaneous vertebroplasty

Vertebroplasty is a minimally invasive treatment method for vertebral body fractures caused by osteoporosis or tumours [37]. It consists in the image-guided percutaneous injection of cement into the vertebral bodies. Subsequent bacterial infection of the operation site is an extremely rare complication, but if the bacterium in question happens to be *Mycobacterium tuberculosis*, the consequences can be severe. Tuberculous spondylitis, also called Pott's disease, is the infection of the vertebrae after haematogenous spread of the pathogen usually from the lung, leading ultimately to tissue necrosis, vertebral collapse and spinal damage [38].

Lai et al. make the effort to carefully review the 0,16% of tuberculous spondylitis cases after vertebroplasty in Taiwan over a five years time course in their study, including detailed accounts on the disease and treatment course of the two patients with the worst and best outcome respectively [39].

In conclusion, he authors advice special caution for subjects with a history of pulmonary tuberculosis or recent contact with active tuberculosis patients as well as an early initiation of anti-tuberculosis treatment if an infection is suspected.

Conflicts of interest

The author declares no conflict of interests.

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